Remarks

In the pending non-final Office Action, claims 20-24, 32 and 43-57 were examined and stand rejected. Applicants herein request reconsideration in light of the amendments above and the following remarks.

Claims 43-57 are rejected under 35 U.S.C. ¶ 112, first paragraph, as not enabled by the specification. From the comments made in the Office Action, it is clear that the rejection is, at least partly, based on the assumption that the present application relates to gene therapy, which would require a showing of therapeutic benefit to be enabled under current Office standards. The claims now pending here, however, relate to a nucleic acid molecule that removes foreign DNA and a method for accomplishing this. The removal is not dependent on expression or functional expression of the foreign DNA, and certainly is not dependent on the ability of this foreign DNA or its removal to cure disease, such as the Office might require to enable a claim to actual gene therapy.

The Office Action has given five main reasons why the claims here pending are not enabled. First, the Office Action asserts that the claims encompass deletion of any nucleic acid sequence from any mouse cell, but the working example teaches only how to remove the neomycin marker gene using a testes-specific promoter. At the time this specification was filed, the skilled person in molecular biology certainly would have been able to construct a cassette which employed any of the known tissue-specific promoters, functionally linked to any gene. The techniques required for performing this type of construction were well-known and quite routine to anyone of ordinary skill. There is no reason, and the Office has provided no reason, why anyone would doubt that the method would work to delete only one particular

gene in one particular tissue when numerous genes are known and numerous tissue-specific promoters are known.

When the prior art considers the methods for making a construct routine, the law does not require the applicant to provide numerous examples using numerous genes and promoters to show numerous constructs in order to enable a method. What is routine in the art preferably is omitted from an application. Moreover, proof of enablement is required only when the Office has advanced reasons adequate to establish that the skilled person could not perform the method in its entire breadth without undue experimentation. M.P.E.P. 2164.02. Therefore, Applicants respectfully submit that the working example provides more than sufficient guidance to enable the person of ordinary skill in the art to make the claimed construct with any known gene or promoter.

Second, the Office asserts that the specification contemplates excising DNA which may include a marker or a wild-type allele in specific somatic tissues, but the specification does not teach how to remove a wild-type allele in somatic cells using the method described. The reason for this conclusion is that only ES cells can undergo the required extensive rounds of selection are required to remove the foreign DNA from a somatic cell and that the somatic cells would have to be selected for in culture, which is not possible. Applicants respectfully submit that this belief evidences a fundamental misunderstanding of this embodiment of the claimed invention.

The specification describes selection in culture for ES cells when the tissue-specific excision is achieved by a gamete-specific promoter. The specification does not state that this selection in culture is required to identify somatic cells that contain the foreign DNA to be removed. According to the

invention, removal of DNA is achieved in the desired somatic cells not because they have undergone multiple rounds of selection in culture to identify them, but because the promoter that controls the excision is active only in those somatic cells. Therefore, as an organism develops and specific tissues differentiate, the tissue-specific promoter will become active and delete the DNA in that tissue. The excision is self-selected according to the type of tissue, not according to artificial selection in culture. Therefore, ability to select somatic cells for removal of the DNA is accomplished by and dependent on the specificity of the promoter. Artificial selection methods in culture are not relevant here.

Applicants therefore respectfully submit that the specification need not "enable" artificial selection of somatic cells to enable the method which is claimed since such selection not only is not claimed but would be completely superfluous and irrelevant to practicing the method.

Third, the Office asserts that it is not clear how a wild-type allele in an organism would be expressed, since the method results in deletion of the construct sequence when the tissue-specific promoter is activated, thus deleting the allele to be expressed. The Office asserts that since the wild-type allele is desired to be "expressed in an organism," its deletion in a particular selected tissue in that organism defeats its expression in the organism.

The methods described and claimed here do not involve or require expression of and deletion of a gene in a whole organism in the way the Office states. A DNA molecule may indeed be expressed in an organism yet be deleted in a specific tissue. The two concepts are not mutually exclusive. Here, a gene is expressed in all other tissues, such as skin, brain, etc., and

thus would be expressed in the organism but not in all tissues of the organism.

Applicants therefore respectfully submit that the Office's concern in this instance is not a realistic one and cannot form a basis for rejection on grounds of enablement.

Fourth, the Office asserts that the foreign DNA to be removed could not be anything other than a marker gene because the cells that express the foreign DNA must be selected for and without a marker one cannot select for the foreign-DNA-containing cells. The Office assumes that only a marker gene can be deleted because only a marker gene can be detected and earmarked for deletion. The Office Action points to Fig. 1, which pictures testes-specific excision of Neo^r. Neither the description of this figure, bridging pages 2-3, nor the figure itself, however, refers to any necessity to select or specifically identify cells for operation of the promoter prior to excision. The excision of the gene is self-excision and occurs in the testes in this example because a testes-specific promoter is controlling the excision.

Furthermore, if the artisan wishes to detect cells that contain the excision cassette DNA, this is easily achieved without resort to expression and detection of a marker gene product. The person of ordinary skill can use appropriate probes using methods well-known in the art and commonly performed. For example, Fig. 2B of the present specification shows a 5' flanking probe that can be used to detect recombination, i.e., presence of the excision cassette.

Because the promoter controlling the operation of the excision cassette is tissue-specific, excision will occur in that tissue specifically. There is no need whatsoever to detect expression of the foreign DNA or even to express it at all in

order to excise it. Applicants therefore respectfully submit that a perceived failure to enable expression and detection of a marker gene is not relevant to this invention when excising a non-marker gene because selection is not a part of the method. Applicant believe that this is not sufficient to base a non-enablement rejection.

Fifth, the Office asserts that regulatable promoters are not enabled because all promoters are regulatable. Since the Office is of the opinion that this term is redundant when applied to promoters, Applicants herein delete this descriptive term without changing the claim scope. Applicants have discussed above why it is not necessary to provide additional working examples to instruct the skilled artisan in how to make and use equivalent constructs that incorporate other promoters with the method. The art is sufficiently advanced and the number available promoters large enough and their action and regulation well-enough understood that incorporating any of them into the present constructs and methods would not involve undue experimentation.

Applicants therefore respectfully submit that this reason also is not sufficient basis for rejection of these claims as not enabled.

For the above-reasons, Applicants request reconsideration of the rejected claims and withdrawal of their rejection.

Claims 43-48 are rejected as indefinite under the standards of 35 U.S.C. ¶ 112, second paragraph. In particular, the Office has pointed to use of the term "foreign," in claim 43, but not in claim 20. It is applicants' position that this term would have been understood by a person of skill in the art at the time this application was filed. However, the claims have been amended to avoid use of this term. No change in scope is intended by these amendments. Other changes to the claims have been made to

simplify the language and improve the readability of the claims. Applicants request that the Office now withdraw this rejection.

The rejection of claims 1-6, 20-24, 32, 38-41, and 43-45 as anticipated by Melchner et al. has been withdrawn.

Claims 20-24, 32 and 43-45 are rejected as anticipated by Russ et al. The Office asserts that Russ et al. teach the generation of a retroviral vector with duplication of terminal control regions U5 and U3 to generate LTRs. The method assertedly uses Cre positioned between two LoxP target sequences to excise most of the sequences unrelated to transcription of U3.

Applicants traverse this rejection. Russ et al. constructed recombinant retrovirus vectors consisting of a copy of Cre under control of an MC promoter, a phosphoglycerate kinase promoter, a LoxP recombinant site and a thymidine kinase-neomycin phosphotransferase fusion gene (tkneo). This construct was used to transfect BOS23 helper cells to produce a recombinant virus to infect NIH 3T3 cells. Once inserted into the 3T3 cells, a sequence containing a phosphoglycerate kinase promoter, a LoxP site, a copy of tkneo, a copy of Cre under control of an MC promoter, a second LoxP site and a second copy of tkneo is formed. None of the vectors in Fig. 1 or of the recombined sequences in Figs. 2-4 of Russ et al. contain, as required by the rejected claims, a recombinase site, a promoter linked to a recombinase gene, the foreign DNA to be excised and a second recombinase site, in that order.

For a reference to anticipate a claim, it must contain, within its four corners, teaching of each and every element required by the rejected claim. Russ et al. do not teach a "molecule comprising in sequential order (a) a recombinase site, (b) a promoter operably linked to, (c) a recombinase gene, (d) the nucleic acid sequence to be removed and, (e) a recombinase

site. Applicants request that the Office reconsider the claims in view of the teachings of Russ et al. and withdraw the rejection of claims 20-24, 32 and 43-45 as anticipated by Russ et al.

Applicants now request favorable consideration of the claims at this time. A fee payment for a three-month extension of time accompanies this paper.

Respectfully submitted,

By _____

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